

Exhibit A

Dkt.#696-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : N. Rosen et al.
U.S. Serial No. : 09/445,054
Filed : March 27, 2000 Examiner: J. Goldberg
Group Art Unit: 1614
For : A METHOD OF TREATING CANCER

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Whitestone, NY 11357

July 26, 2002

Commissioner for Patents and Trademarks
Washington, D.C. 20231

Sir:

**AMENDMENT RESPONSE TO APRIL 26, 2002 FINAL OFFICE
ACTION AND NOTICE OF ASSOCIATE POWER OF ATTORNEY,
NEW ATTORNEY DOCKET AND CORRESPONDENCE ADDRESS**

This Amendment is submitted in response to April 26, 2002 Final Office Action which was issued by the United States Patent and Trademark Office in connection with the above-identified application. The deadline for filing a response is April 26, 2002. Therefore, this Amendment is being timely filed.

Please amend the above-identified application as follows:

In the Claims:

Please cancel claims 1-3, 9-11, 27, 31 and 33-39 without prejudice and add the following new claims:

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40. (New) A method for achieving a synergistic therapeutic effect in a mammal in need thereof which comprises administering to said mammal amounts of at least two therapeutic agents selected from a group consisting of:

- a) a prenyl-protein transferase inhibitor and
- b) an antineoplastic agent which is a microtubule-stabilizing agent;

wherein the synergistic therapeutic effect is the treatment of cancers of the brain, breast, colon, genitourinary tract, lymphatic system, pancreas, rectum, stomach, larynx, liver, lung, prostate, stet histiocytic lymphoma lung adenocarcinoma, pancreatic carcinoma, colo-rectal carcinoma, small cell lung cancers and neurological tumor cancer whose growth is inhibited by the administration of the prenyl-protein transferase inhibitor and the antineoplastic agent.

41. (New) The method according to Claim 40 wherein an amount of a prenyl-protein transferase inhibitor and an amount of a microtubule-stabilizing agent are administered simultaneously.

42. (New) The method according to Claim 40 wherein an amount of a microtubule-stabilizing agent and an amount of a prenyl-protein transferase inhibitor are administered consecutively.

43. (New) The method according to Claim 40 wherein the antineoplastic agent is selected from: paclitaxel, epothilone A, epothilone B, desoxyepothilone A and desoxyepothilone B.

44. (New) The method according to Claim 40 wherein the prenyl-protein transferase inhibitor is selected from:

2(S)-Butyl-1-(2,3-diaminoprop-1-yl)-1-(1-naphthoyl)piperazine;

1-(3-Amino-2-(2-naphthylmethylamino)prop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

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~~2(S)-Butyl-1-{5-[1-(2-naphthylmethyl)]-4,5-dihydroimidazol}methyl-4-(1-naphthoyl)piperazine;~~

~~1-[5-(1-Benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine;~~

~~1-{5-[1-(4-nitrobenzyl)]imidazolymethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine;~~

~~1-(3-Acetamidomethylthio-2(R)-aminoprop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;~~

~~2(S)-Butyl-1-[2-(1-imidazolyl)ethyl]sulfonyl-4-(1-naphthoyl)piperazine;~~

~~2(R)-Butyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;~~

~~2(S)-Butyl-4-(1-naphthoyl)-1-(3-pyridylmethyl)piperazine;~~

~~1-2(S)-butyl-(2(R)-(4-nitrobenzyl)amino-3-hydroxypropyl)-4-(1-naphthoyl)piperazine;~~

~~1-(2(R)-Amino-3-hydroxyheptadecyl)-2(S)-butyl-4-(1-naphthoyl)-piperazine;~~

~~2(S)-Benzyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;~~

~~1-(2(R)-Amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;~~

~~1-(2(R)-Amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine;~~

~~2(S)-Butyl-1-[(4-imidazolyl)ethyl]-4-(1-naphthoyl)piperazine;~~

~~2(S)-Butyl-1-[(4-imidazolyl)methyl]-4-(1-naphthoyl)piperazine;~~

~~2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl]acetyl-4-(1-naphthoyl)piperazine;~~

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2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl]ethyl]-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-hydroxypropyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-4-hydroxybutyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2-Amino-3-(2-benzyloxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2-Amino-3-(2-hydroxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-[3-(4-imidazolyl)propyl]-2(S)-butyl-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-4-(2,3-dimethylphenyl)-1-(4-imidazolylmethyl)-piperazin-5-one;

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one;

1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(1-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-methoxybenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(3-methyl-2-butenyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

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2(S)-*n*-Butyl-1-[1-(4-fluorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

1-[1-(4-Bromobenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethylbenzyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-1-[1-(4-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-1-[1-(3-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

1-[1-(4-Phenylbenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-phenylethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethoxy)imidazol-5-ylmethyl]piperazine;

1-{{1-(4-cyanobenzyl)-1H-imidazol-5-yl}acetyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(methanesulfonyl)ethyl]-2-piperazinone;

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)ethyl]-2-piperazinone;

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(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[N-ethyl-2-acetamido]-2-piperazinone;

(±)-5-(2-Butynyl)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

5(S)-Butyl-4-[1-(4-cyanobenzyl-2-methyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-piperazin-2-one;

4-[1-(2-(4-Cyanophenyl)-2-propyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-5(S)-(2-methylsulfonyl)ethyl)piperazin-2-one;

5(S)-n-Butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2-methylphenyl)piperazin-2-one;

4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-5(S)-(2-fluoroethyl)-1-(3-chlorophenyl)piperazin-2-one;

4-[3-(4-Cyanobenzyl)pyridin-4-yl]-1-(3-chlorophenyl)-5(S)-(2-methylsulfonyl)ethyl)-piperazin-2-one;

4-[5-(4-Cyanobenzyl)-1-imidazolylethyl]-1-(3-chlorophenyl)piperazin-2-one;

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyl-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyl-2-methyl-3-phenylpropionyl-homoserine lactone,

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2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-4-pentenoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-4-pentenoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxypentanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxypentanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]5-pentyloxy-4-methylpentanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-4-methylpentanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methylbutanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methylbutanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylbutanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylbutanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylthio-2-methyl-3-phenylpropionyl-homoserine lactone,

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2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylthio-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine methyl ester,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone (Compound A),

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-naphth-2-yl-propionyl-methionine sulfone methyl ester,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-naphth-2-yl-propionyl-methionine sulfone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone methyl ester,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone,

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2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylloxy-3-methylbutanoyl-methionine methyl ester.

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylloxy-3-methylbutanoyl-methionine,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)methyl]pentylloxy-3-phenylpropionyl-homoserine lactone,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylloxy-3-phenylpropionyl-homoserine,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)methyl]pentylloxy-3-methylbutanoyl-methionine methyl ester

1-(4-Biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Cyanobenzyl)-5-(4'-phenylbenzamido)ethyl-imidazole

1-(2'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Biphenylethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Bromo-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Trifluoromethoxy-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-(3',5'-dichloro)-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Methoxy-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

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1-(4-(3',5'-Bis-trifluoromethyl)-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(2'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)-4-methylimidazole
 1-(4-Biphenylmethyl)-5-(4-cyanophenoxy)-imidazole
 5-(4-Cyanophenoxy)-1-(2'-methyl-4-biphenylmethyl)-imidazole
 5-(4-Biphenyloxy)-1-(4-cyanobenzyl)-imidazole
 5-(2'-Methyl-4-biphenoxy)-1-(4-cyanobenzyl)-imidazole
 5-(4-(3',5'-dichloro)biphenylmethyl)-1-(4-cyanobenzyl)imidazole
 1-(4-biphenylmethyl)-5-(1-(R,S)-acetoxy-1-(4-cyanophenyl)methyl)imidazole
 1-(4-Biphenylmethyl)-5-(1-(R,S)-hydroxy-1-(4-cyanophenyl) methyl)imidazole
 1-(4-Biphenylmethyl)-5-(1-(R,S)-amino-1-(4-cyanophenyl) methyl)imidazole
 1-(4-biphenylmethyl)-5-(1-(R,S)-methoxy-1-(4-cyanophenyl)-methyl)imidazole
 1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(4-biphenyl)-methyl imidazole
 1-(4-Cyanobenzyl)-5-(1-oxo-1-(4-biphenyl)-methyl imidazole
 1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(3-fluoro-4-biphenyl)-methyl)- imidazole
 1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(3-biphenyl)methyl-imidazole
 5-(2-[1,1'-Biphenyl]vinylene)-1-(4-cyanobenzyl)imidazole
 1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)amino]-3-methoxy-4-phenylbenzene
 1-(4-Biphenylmethyl)-5-(4-bromophenoxy)-imidazole

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1-(3'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(4'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(3'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(4'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(3'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(4'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(2'3'-Dichloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(2'4'-Dichloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(2'5'-Dichloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(3'-Trifluoromethoxy-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(2'-Fluoro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(4-(2'-Trifluoromethylphenyl)-2-Chlorophenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-{1-(4-(2'-trifluoromethylphenyl)phenyl)ethyl}-5-(4-cyanobenzyl) imidazole
 1-(2'-Trifluoromethyl-4-biphenylpropyl)-5-(4-cyanobenzyl) imidazole
 1-(2'-N-t-Butoxycarbonylamino-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(2'-Aminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
 1-(2'-Acetylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

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1-(2'-Methylsulfonylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)
imidazole

1-(2'-Ethylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Phenylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Glycylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Methyl-4-biphenylmethyl)-2-chloro-5-(4-cyanobenzyl) imidazole

1-(2'-Methyl-4-biphenylmethyl)-4-chloro-5-(4-cyanobenzyl) imidazole

1-(3'-Chloro-2-methyl-4-biphenylmethyl)-4-(4-cyanobenzyl)imidazole

1-(3'-Chloro-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3'-Trifluoromethyl-2-methyl-4-biphenylmethyl)-4-(4-cyanobenzyl)
imidazole

1-(3'-Trifluoromethyl-2-methyl-4-biphenylmethyl)-5-(4-
cyanobenzyl)imidazole

1-(3'-Methoxy-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Chloro-4'-fluoro-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Ethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-(2-Propyl)-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-(2-Methyl-2-propyl)-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Ethyl-4-biphenylmethyl)-5-(4-(1H-tetrazol-5-yl))benzyl)imidazole

1-[1-(4-Cyanobenzyl)imidazol-5-ylmethoxy]-4-(2'-methylphenyl)-2-(3-N-
phthalimido-1-propyl)benzene

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1-(3',5'-Ditrifluoromethyl-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3',5'-Chloro-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3',5'-Dimethyl-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-(N-Boc-aminomethyl)-4-biphenylmethyl)-5-(4-cyanobenzyl)-imidazole

1-(3-Aminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Cyanobenzyl)-2-methyl-5-(2'-methylbiphenyl-4-yloxy)imidazole
5-(4-Cyanobenzyl)-1-(3-cyano-2'-trifluoromethylbiphenyl-4-ylmethyl)-imidazole

2-Amino-5-(biphenyl-4-ylmethyl)-1-(4-cyanobenzyl)imidazole

2-Amino-1-(biphenyl-4-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Butylbiphenyl-4-ylmethyl)-5-(4-cyanobenzyl)-imidazole

1-(3-Propylbiphenyl-4-ylmethyl)-5-(4-cyanobenzyl)-imidazole

1-(4-Biphenylmethyl)-4-(4-cyanobenzyl-2-methylimidazole

1-(4-Cyanobenzyl)-5-[(3-fluoro-4-biphenyl)methyl]imidazole

1-(4-Cyanobenzyl)-5-[1-(4-biphenyl)-1-hydroxy]ethyl-2-methylimidazole

1-(4-Cyanobenzyl)-5-(4-biphenylmethyl)-2-methylimidazole

1-(4-Cyanobenzyl)-5-[1-(4-biphenyl)]ethyl-2-methyl imidazole

1-(4-Cyanobenzyl)-5-[1-(4-biphenyl)]vinylidene-2-methylimidazole and

1-(4-Cyanobenzyl)-5-[2-(4-biphenyl)]vinylene-2-methylimidazole

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1-(4-[Pyrid-2-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole
1-(4-[3-Methylpyrazin-2-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole
1-(4-(Pyrimidinyl-5-yl)phenylmethyl)-5-(4-cyanobenzyl)imidazole
1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
1-(2-Phenyl-N-Oxopyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
1-(3-Phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
1-(3-Phenyl-N-Oxopyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
1-(2-(3-Trifluoromethoxyphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
1-(2-(2-Trifluoromethylphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
1-(3-Phenyl-2-Chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
1-(3-Phenyl-4-chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
1-(2-Amino-3-phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
1-(2-[Pyrid-2-yl]pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
N-{1-(4-Cyanobenzyl)-1H-imidazol-5-yl)methyl}-5-(pyrid-2-yl)-2-amino-pyrimidine
N,N-bis(4-Imidazolemethyl)amino-3-[(3-carboxyphenyl)oxy]benzene
N,N-bis(4-Imidazolemethyl)amino-4-[(3-carboxyphenyl)oxy]benzene
N,N-bis(4-Imidazolemethyl)amino-3-[(3-carbomethoxyphenyl)-oxy]benzene
N,N-bis(4-Imidazolemethyl)amino-4-[(3-carbomethoxyphenyl)-oxy]benzene

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N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)aminomethyl-3-[(3-carboxyphenyl)oxy]benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)aminomethyl-3-[(3-carbomethoxyphenyl)oxy]benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-3-(phenoxy)benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-4-(phenoxy)benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-4-(phenylthio)benzene

N-Butyl-*N*-[1-(4-cyanobenzyl)-5-imidazolemethyl]amino-4-(phenoxy)benzene

N-[1-(4-Cyanobenzyl)-5-imidazolemethyl]amino-4-(phenoxy)benzene

N-(4-Imidazolemethyl)amino-3-[(3-carboxyphenyl)oxy]benzene

1-[*N*-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-*N*-(4-cyanobenzyl)amino]-4-(phenoxy)benzene

(±)-4-[(4-imidazolylmethyl)amino]pentyl-1-(phenoxy)benzene

1-[*N*-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-*N*-(*n*-butyl)amino)methyl]-4-(phenoxy)benzene

4-[*N*-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-*N*-(*n*-butyl)amino]-1-(phenylthio)benzene

(±)-4-[*N*-(1-(4-cyanobenzyl)-4-imidazolylmethyl)-*N*-(*n*-butyl)amino]-1-(phenylsulfinyl)benzene

3-[*N*-(4-imidazolylmethyl)-*N*-(*n*-butyl)amino]-*N*-(phenyl)benzenesulfonamide and

1-[*N*-(1-(4-cyanobenzyl)-5-imidazolylmethyl)amino]-3-methoxy-4-phenylbenzene

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4-{3-[4-(-2-Oxo-2-H-pyridin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl}benzonitrile

4-{3-[4-3-Methyl-2-oxo-2-H-pyridin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl}benzonitrile

4-{3-[4-(-2-Oxo-piperidin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl}benzonitrile

4-{3-[3-Methyl-4-(2-oxopiperidin-1-yl)-benzyl]-3-H-imidazol-4-ylmethyl}-benzonitrile

(4-{3-[4-(2-Oxo-pyrrolidin-1-yl)-benzyl]-3H-imidazol-4-ylmethyl}-benzonitrile

4-{3-[4-(3-Methyl-2-oxo-2-H-pyrazin-1-yl)-benzyl]-3-H-imidazol-4-ylmethyl}-benzonitrile

4-{3-[2-Methoxy-4-(2-oxo-2-H-pyridin-1-yl)-benzyl]-3-H-imidazol-4-ylmethyl}-benzonitrile

4-{1-[4-(5-Chloro-2-oxo-2H-pyridin-1-yl)-benzyl]-1H-pyrrol-2-ylmethyl}-benzonitrile

4-[1-(2-Oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile

4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile

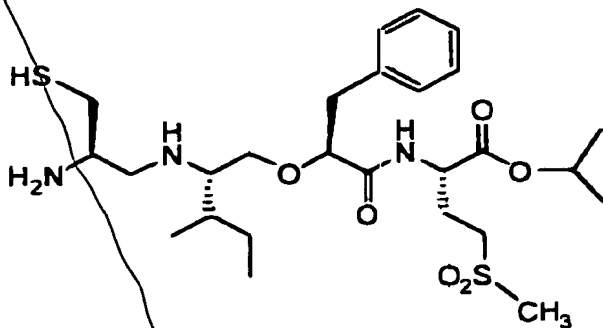
4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydropyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

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45. (New) The method according to Claim 40 wherein the prenyl-protein transferase inhibitor is selected from:

2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A)



1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile and

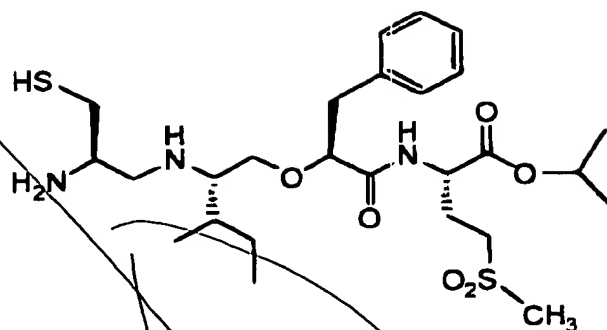
1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene

or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

46. (New) The method according to Claim 40 wherein the antineoplastic agent is paclitaxel and the prenyl-protein transferase inhibitor is

2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A)

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47.(New) A pharmaceutical composition comprising an amount of a prenyl-protein transferase inhibitor and an amount of an antineoplastic agent which is a microtubule-stabilizing agent, the composition which is effective for treating cancer in a mammal in need thereof.

48.(New) A method of preparing a pharmaceutical composition which comprises mixing an amount of a prenyl-protein transferase inhibitor and an amount of an antineoplastic agent which is a microtubule-stabilizing agent.

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REMARKS

By this amendment, applicants have cancelled claims 1-3, 9-11, 27, 31 and 3-39 without prejudice and added claims 40-48. Applicants maintain that new claims 40-48 are well supported by the specifications as originally filed. Accordingly, applicants respectfully request the entry of this amendment.

Applicants believe that all the new claims 40-48 have obviated all grounds of objections/rejections raised in the April 26, 2002 Final Office Action.

Applicants maintain that the prenyl-protein transferase inhibitor and an antineoplastic agent which is a microtubule-stabilizing agent are fully enabled since both the inhibitor and the agents are described in the specifications. More importantly, the assays for the activity of either the inhibitor or either the agents have been fully described in the specifications. Accordingly, an ordinary skilled artisan had been enabled to make a claimed inhibitor/agent.

Applicants believe that the newly presented claims are in conditions for allowance and respectfully urge the examiner to reconsider and withdraw all objections/rejections raised in the April 26, 2002 Final Office Action.

Associate Power of Attorney, New Attorney Docket Number and Correspondence Address

Applicants attach hereto as **Exhibit A**, an Associate Power of Attorney. Applicant, respectfully request that the attorney docket be changed to **696-US** and request that all future correspondence be sent to the below address:

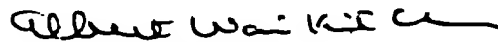
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If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,



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